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EDITORIAL VIEWPOINT

Resolution of Inflammation, Statins, and Plaque Regression*

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The success of aggressive pharmacological therapy in the prevention and treatment of cardiovascular disease continues to give us renovated energy and constructive hope. Within the last decade, the incidence of acute myocardial infarction in the U.S. population showed a steady decrease. Ten years ago, in 2002, the annual hospitalization rate was 1,131

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per 100,000 Medicare beneficiaries. This number fell to 866 in 2007, a 23% decline (1). Other studies have confirmed this observation (2), with an impressive 31% reduction in death attributable to cardiovascular disease from 1998 to 2008 (3). Despite these improvements, cardiovascular disease continues to be the major cause of death in developed countries, and atherothrombosis is responsible for the majority of these events.

Atherothrombosis and High-Risk Plaques

Vulnerable plaques are the main cause of thrombosis and are characterized by large atheroma volume, increased necrotic core, reduced fibrous cap thickness, and inflammation. Establishing which of these high-risk features will trigger acute coronary syndromes (ACS) became possible by applying novel imaging techniques to prospective human studies. Using computed tomography angiography, Motoyama et al. (4) identified 2 important features in the development of ACS: positive remodeling (large atheroma volume), and low attenuation plaques (increased necrotic core). An impressive 22% event rate was documented for plaques with both features. On the optimistic side, the incidence was only 4.4% of the population studied. Most importantly, when treated with statins, these low attenuated plaques showed significant reductions in atheroma volume (5). Using a more invasive approach, the PROSPECT (Providing Regional Observations to Study Predictors of Events in the Coronary Tree) study (6) identified 3 independent predictors for future cardiovascular events in nonobstructive coronary lesions from patients with ACS. These predictors included thin-cap fibroatheroma, plaque burden $>70\%$, and minimal luminal area <4 mm^2. A 17% event rate was documented for plaques with all 3 features. The incidence was 4.2% of the population studied, remarkably similar to the 4.4% previously identified in the Motoyama study (4). These crucial data of natural history were obtained by a combination of computed tomography angiography, intravascular ultrasound, and backscattered intravascular ultrasound analysis, also known as virtual histology. We learned that although infrequent, identification of very high-risk plaques is of significant clinical relevance, but will require simultaneous, multiple imaging technology (7).

Considering the limitations in imaging resolution, only a few studies evaluated fibrous cap thickness in vivo (8). However, it is clear that ACS results from fibrous plaque digestion and rupture, mostly by activated macrophages. Also known as the "Achilles heel" of the plaque, this rim of collagen is the last barrier between stability and thrombosis. Fibrous cap integrity consolidates the difference between life and death in patients with high-risk atherosclerosis. Nevertheless, studies analyzing fibrous cap response to therapy are lacking.

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The Present Study

In this issue of *iJACC*, Hattori et al. (9) contribute to current knowledge providing evidence of the effects of statins on the fibrous cap in human coronary atheroma. Careful structural analysis of coronary plaques using multimodality imaging technology before and after 9 months of pitavastatin therapy was performed. Grayscale and integrated-backscattered intravascular ultrasound, and optical coherence tomography documented significant reductions in percentage of plaque volume index, percentage of lipid volume index, and a significant increase in fibrous cap thickness, respectively. Pitavastatin was associated with a 6% reduction in plaque volume index. This reduction in atheroma volume is higher than expected for a U.S. population using an atorvastatin-like medication with a mean low-density lipoprotein cholesterol plasma level of 89 ± 23 mg/dl at follow-up. Nevertheless, these results go along with previously observed reductions in atheroma volume using the same medication in the Japanese population (10). The investigators also documented a 6% reduction in lipid volume with similar increase in fibrous volume index (9). Of significant relevance, paired optical coherence tomography analysis before and after pitavastatin documented an increase of 52 ± 32 μm in fibrous cap thickness. These changes in cap thickness involve a newly synthesized extracellular matrix, probably mediated by synthesis of reparative type III collagen (Fig. 1). Increases in cap thickness, in conjunction with changes in lipid volume constitute major advances in the field, but should be evaluated in conjunction with the evidence documented in previously published studies.

Statin Therapy, Atheroma Volume, and Changes in Plaque Composition

Within the last decade, statins have been shown to reduce plaque burden in a number of imaging studies. Corti et al. (11) documented significant reductions in carotid lesions using magnetic resonance imaging in patients treated with high dose–simvastatin. The REVERSAL (Reversal of Atherosclerosis with Aggressive Lipid Lowering) study documented a beneficial effect of high-dose atorvastatin showing stabilization of the disease, compared with a statistically significant progression of atheroma volume (+ 2.7%) in the control group (12). In addition, the ASTEROID (Study to Evaluate the Effect of Rosuvastatin on Intravascular Ultrasound-Derived Coronary Atheroma Burden) study documented a median 6.8% reduction in atheroma volume in ACS patients treated with 40 mg of rosuvastatin daily (13). More recently, the SATURN (Study of Coronary Atheroma by Intravascular Ultrasound: Effect of Rosuvastatin versus Atorvastatin) study documented 1.22% to 0.99% reductions in percentage of atheroma volume for both medications, respectively (14). Plaque regression was seen in the majority of patients, 68% and 63%, respectively. Despite the small reductions in percentage of atheroma volume, the changes in plaque composition may have a much more relevant role clinically. In the SATURN study, the incidence of death and acute myocardial infarction was only 1.9% for both medications (14).

The histological effects of statins in human atheroma were evaluated by Crisby et al. (15) in carotid plaques 3 months before carotid endarterectomy. They found decreased lipid oxidation, inflamma-

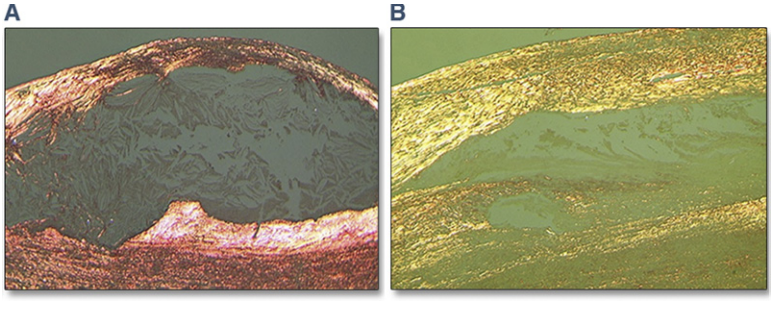

Figure 1. Polarized Microscopy With Picrosirius Red Staining To Characterize Fibrous Cap Thickness and Collagen Composition in Human Aortic Plaques

(A) Thin-cap fibroatheroma mostly composed by structural, type I collagen stained in **red color. (B)** Thick cap fibroatheroma mostly composed by reparative, type III collagen recently synthesized as a healing response to injury. Courtesy of K. Raman Purushothaman, MD, Mount Sinai Hospital, 2011; used with permission.

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tion, matrix metalloproteinase-2, and cell death in plaques from patients taking the medication. In addition, increased tissue inhibitor of metalloproteinase-1, and collagen content was also documented, confirming plaque-stabilizing effects in humans. More recently, Puato et al. (16) studied cellular changes using the same protocol. Significant reductions on macrophage infiltration along with increases in smooth muscle cells were documented with just 3 months of high-dose statin therapy (16).

Mechanisms of Plaque Regression: Resolution of Inflammation and Efferocytosis

Monocytes-derived macrophages are responsible for disease progression, and their role in plaque regression is evolving rapidly. Monocytes can differentiate into those that promote inflammation, which are referred to as classically activated (M1) macrophages, and those than promote resolution of inflammation and collagen synthesis, also referred as alternatively activated (M2) macrophages (17). Supported by T-helper 1 lymphocytes (hence the name M1 macrophages), these proinflammatory phagocytes are associated with insulin resistance, secretion of matrix metalloproteinases, thinning of fibrous cap, and plaque rupture. In contrast, M2 macrophages are supported by T-helper 2 lymphocytes, and are associated with insulin sensitivity, removal of apoptotic bodies from the plaque (efferocytosis), and collagen synthesis by transforming growth factor beta–mediated activity (17).

In the atherosclerotic lesions of apolipoprotein E (ApoE)$^{-/-}$ mice, resolution of inflammation is not observed in the setting of hypercholesterolemia. However, when plaques are exposed to low levels of cholesterol, plaque regression occurs. In this model of atherosclerosis, exposure to low cholesterol can be obtained by: 1) transplantation of plaque-bearing aortae from the ApoE$^{-/-}$ mice into wild-type mice (18); and 2) treatment with ApoE encoding adenoviral vectors, which normalize plasma cholesterol to wild-type levels and increase high-density lipoprotein levels 4-fold (19). Using the transplant model, inflammatory cell egression, and efferocytosis of apoptotic bodies has been carefully studied. Dendritic cells migrate through adventitial lymph vessels to local lymph nodes in a process that is dependent on the chemotactic ligands of the G protein-coupled chemokine receptor-7 (CCR7) (20). A series of insightful observations in this transplant model promoted CCR7 as *the* pivotal molecule of plaque regression (21). The molecular mechanisms involved the liver X receptor (responsible for the high-density lipoprotein–dependent reverse cholesterol transport), the MERTK engulfment receptor, and others (22,23). Using this transplant model, atorvastatin and rosuvastatin promoted clusters of differentiation CD68+ cell emigration, increasing transcriptional activity and chromatin organization at the CCR7 promoter (24). Simultaneously, the ApoE-encoding adenoviral vector model identified a different pattern of macrophage removal in the ApoE$^{-/-}$ mice model (25). Within 4 weeks of therapy, esterified cholesterol was significantly reduced. This was followed by a 72% reduction in macrophage content *independent* of CCR7. Most importantly, a marked inhibition of macrophage recruitment from circulating monocytes was achieved by significant reductions in endothelial adhesion molecules (25). As a result, suppressed monocyte recruitment, rather than CCR7 efferocytosis, may be the predominant mechanism in plaque regression. In the absence of macrophage egression, local proliferation of M2 macrophages may be responsible for clearance of apoptotic cells and transforming growth factor beta–mediated collagen synthesis (26).

Conclusions

The understanding of major reductions in coronary events associated with aggressive medical therapy is evolving rapidly. High-dose statin therapy is associated with beneficial histological changes in plaque composition in humans. As a result, plaque regression is now carefully documented in vivo by multimodality novel imaging technology. The cellular and molecular mechanisms responsible for plaque regression in humans are less understood, but clearly involve inhibition of macrophage recruitment, resolution of inflammation, and new collagen synthesis. More studies are needed to clearly elucidate this issue.

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